Myotonia

A Review of Its Clinical Implications

Discussions by GAURANG P. BHATT, M.D., NAZHIYATH VIJAYAN, M.D., PIERRE M. DREYFUS, M.D.

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DR. DREYFUS: THE SYMPTOMS AND SIGNS of muscle disease, particularly when they are mild or evanescent, can easily be misinterpreted, with inappropriate medical treatment resulting.

Myotonia, when elicited, is frequently and erroneously considered symptomatic of irreversible muscle damage, when in fact it may be a sign of a benign or treatable condition. It seems therefore appropriate to review the clinical significance, pathophysiologic factors and therapy of this condition.

Myotonia can be defined as a state of increased muscle tone which results from active contraction and which perseverates for an unusually long time. The patient complains of exaggerated spasm or "cramp" of a group of muscles and the subsequent inability to relax these muscles. Whereas cold, excitement and vigorous exercise tend to aggravate myotonia, repetitive contractions may enhance relaxation and decrease the spasm.

On clinical examination, myotonia can be elicited by instructing the patient to grip the examiner's hand forcefully and then to let go as promptly as possible (hand grasp test). In the presence of myotonia percussion of the thenar eminence brings about opposition of the thumb, and relaxation of muscle contraction is slow. Percussion of the tongue against a tongue depressor causes a persistent dimpling of the surface (percussion myotonia). This phenomenon should be distinguished from myoedema, a local bulge induced by tapping a muscle of a cachectic patient. Whereas the muscles of patients afflicted with myotonia may appear to be large, their strength tends to be reduced. Electrical stimulation of the muscles brings about an exaggerated response followed by slow relaxation. Figure 1 compares the electromyographic responses recorded in other pathological states with the response found in myotonia. When the response is electronically translated into noise, it sounds like a "dive bomber."

Dr. Bhatt will now present a case in which myotonia constituted the main symptom.

Dr. Bhatt: A 16-year-old high school boy was admitted to the hospital with the chief complaint of muscle stiffness. At the age of eight the patient first noticed that he had trouble starting to run. After running a short distance his muscles would stiffen and start to ache, but if he persisted in his efforts the ache and stiffness would disappear. Even at rest his muscles often felt "tight." Occasionally when he tried to run the muscle stiffness

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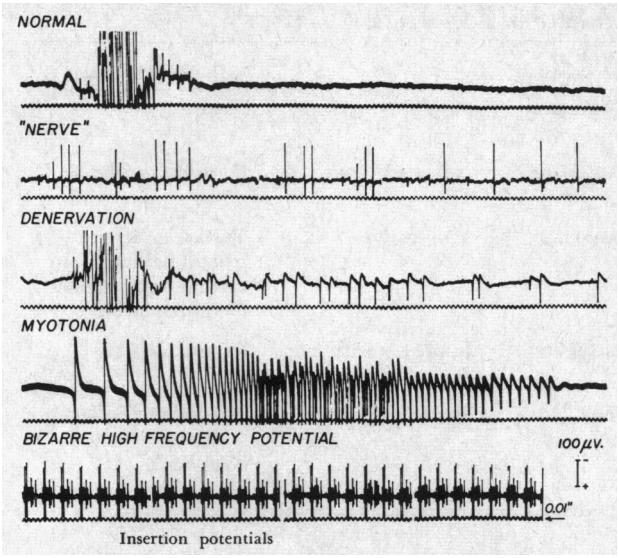

Figure 1.—Electromyographic recordings of normal, denervated and myotonic muscle. Delayed relaxation is exemplified by the prolonged persistence of electrical activity.

caused him to fall. The "tightness" of muscle was not affected by sudden exposure to cold temperatures and the patient's muscle power remained normal. By the age of 16 he was able to lift 100 pounds over his head. Over the years, muscle stiffness gradually worsened. The patient denied visual, sensory or other neurological symptoms. His scholarship in school was always above average. Past medical history and review of systems was unremarkable. Since the patient was an adopted child, family history was virtually impossible to obtain. The only known relative was a sibling who was said to be completely normal.

General physical examination was within normal limits. Neurological examination revealed an alert, oriented and cooperative boy with normal memory and intelligence. The results of examination of the cranial nerves were normal with the exception of the finding of lid myotonia: When the patient was asked to look suddenly at the floor after he had been staring at the ceiling, the upper lids remained elevated and relaxed slowly. Tongue, grip and percussion myotonia of other muscles was easily elicited. The patient's muscles were generally hypertrophied, but exhibited normal power and coordination. Reflexes were symmetrical and no pathological reflexes could be elicited. Sensory examination revealed normal findings.

The results of the following laboratory investigations were all within normal limits: hemoglobin, white blood cell count and differential, sedimentation rate, serology, urinalysis, serum electrolytes, serum calcium, phosphorus, fasting and two-hour post-prandial blood sugar, total protein, protein and immuno-electrophoresis, serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatine phosphokinase (CPK). Chest films and electrocardiogram were normal. Slitlamp examination showed no evidence of cataracts. The electromyogram showed a somewhat increased insertional activity, no fibrillations, no positive sharp waves or fasciculations and a normal interference pattern. The typical "dive bomber" sound was obtained (Figure 1). Potassium loading with 7.5 grams of KCl failed to produce weakness.

Dilantin, 100 mg three times a day, was prescribed. Within two weeks after this therapy was begun the patient showed a remarkable decrease in muscle stiffness and myotonia.

It is unfortunate that a family history could not be obtained in the case of this patient. The presence of myotonia without paroxysmal or progressive weakness, the absence of wasting and the lack of any other stigmata of myotonic dystrophy (cataracts, baldness and testicular atrophy) and the negative potassium loading test confirmed the diagnosis of myotonia congenita. A somewhat atypical feature of this case was the fact that myotonia was not aggravated by exposure to cold.

Dr. Dreyfus: Thank you, Dr. Bhatt. Dr. Vijayan, would you review the various disease entities in which myotonia may be elicited?

Dr. Vijayan: One can identify three disease entities in which myotonia is a major clinical manifestation (Table 1). These are: (1) myotonia congenita, sometimes known as Thomsen's disease; (2) paramyotonia congenita of von Eulenberg; and (3) myotonic dystrophy. In addition, there is a group of muscle diseases associated with myotonia which may be placed into the general category of myotonia acquisita. The various myotonic syndromes are easily and readily distinguished on clinical grounds.

Myotonia congenita. As the term implies, this disorder is present at birth. Although it is transmitted by an autosomal dominant gene, it may have recessive characteristics. Affected infants may manifest a "strangled cry," and this may be associated with feeding difficulties. Developmental milestones are frequently delayed. In

TABLE 1.—*Diseases Associated with Myotonia*

Type	*Age of Onset*	*Mode of Inheritance*	*Prognosis*	*Associated Findings*
Myotonia congenita (Thomsen)	Birth	Dominant	Non-progressive	None
Paramyotonia (von Eulenberg)	Childhood, adolescence	Dominant	Non-progressive	Periodic paralysis
Dystrophia myotonica (Steinert)	Late adolescence and early adult life	Dominant	Progressive	Testicular atrophy frontal baldness cardiac involvement mental deficiency
Hyperkalemic periodic paralysis	Childhood to early adult life	Dominant	Improves with age	Paramyotonia
Polymyositis	Any age	None	Variable	Generalized collagen disease Neoplasia Skin rash

general, myotonia is diffuse, involving all of the voluntary muscles. As the patient develops and grows older, muscles may become hypertrophic and the myotonia tends to decrease in severity. Myotonia may worsen on exposure to cold while it improves with exercise, although in some cases it may be aggravated by exercise, a phenomenon referred to as "myotonia paradoxa." Generally speaking, myotonia is not associated with severe pain or cramps, as is the case in myopathy associated with a lack of myophosphorylase (McArdle's disease) and other enzymatic deficiencies. As a rule dystrophic features do not develop in patients with myotonia congenita and the disease runs a benign course.

Histopathological examination of muscle fibers shows diffuse hypertrophy. Except for large and elaborate end-plates, which are supposed to be characteristic of this condition, no specific pathological changes can be discerned. The muscle enzymes are not elevated in the serum, except in rare and severe cases, in which serum aldolase may be elevated.

Another disease entity associated with myotonia in infancy was described by Schwartz and Jampel in 1962.[1] This is a familial disorder characterized by myotonia, short stature, a variety of skeletal anomalies, especially hip dysplasia, and unusual facial and ocular abnormalities. Most of the afflicted children have diffuse muscular hypertrophy. The mode of inheritance of this disorder has not as yet been worked out.

Paramyotonia congenita. In this benign disease entity, the myotonia becomes evident on exposure to cold. The distinguishing feature of this disorder is the occurrence of episodic flaccid paralysis similar to that seen in periodic paralysis. Most of the cases have associated hyperkalemia during the paralytic attacks and some investigators[2] consider hyperkalemic periodic paralysis and paramyotonia congenita to be one and the same disease entity. Myotonia tends to be restricted to the lids, the tongue, the face or the distal parts of the extremities. It is not uncommon to elicit a history of myotonia of the tongue precipitated by licking an ice cream cone. Dystrophic changes do not develop. The trait is transmitted in an autosomal dominant manner which has almost 100 percent penetrance in both sexes. No specific histopathological changes have been described.

Myotonic dystrophy. This disease tends to begin in adolescence or early adult life. The clinical presentation is quite variable from family to family and from generation to generation in the same family. Myotonic dystrophy may start with myotonia, then is followed in time by atrophy and weakness of muscles as well as by systemic dystrophic manifestations. Quite frequently the earliest muscles to be involved are those of the face and neck or the peripheral muscles of the extremities. Mild ptosis and lack of facial expression may be present for a long time before any other changes become evident. Since the masseter and the sternocleidomastoid muscles are commonly involved, the patient's neck may appear to be thin, with an exaggerated forward curvature sometimes referred to as "swan neck." Partial ptosis of the lids is almost always present and in

50 percent of cases the external ocular muscles are also involved. As the disease progresses, dysarthria and dysphagia develop due to involvement of the laryngeal and pharyngeal muscles. While myotonia can best be demonstrated in the thenar muscles by percussion or the "hand-grip test," it is electromyographically obvious in all the involved muscles. In the latter phases of the disease, at a point when muscle atrophy is extensive, clinical myotonia may no longer be elicited. Unlike myotonia and paramyotonia congenita, myotonic dystrophy is a progressive disease with a slow downhill course which leads to severe disability within 15 to 20 years from the onset.

Dystrophic manifestations in nonmuscular tissue consist of cataracts in 42 percent of patients, frontal baldness in 44 percent, testicular atrophy in 70 percent of males and a variety of sexual disorders in 64 percent of females.[3,4] A fairly large proportion of patients with myotonic dystrophy, and some of their unaffected siblings, have associated mental deficiency. Cardiac involvement is quite common and can be held responsible for sudden death. Electrocardiographic changes are present in 90 percent of cases in the late stages of the illness.

Although significant endocrine and metabolic changes have been described in association with myotonic dystrophy, no definite clinical correlation has been possible. In patients with testicular atrophy, the seminiferous tubules closely resemble those seen in Klinefelter's syndrome, but the nuclear sex chromatin pattern is normal. The various other changes frequently noted are a low basal metabolic rate, hypothyroidism, diabetes mellitus, reduced 17-oxysteroid excretion and increased levels of interstitial cell stimulating as well as luteotropic hormones. The latter changes are not observed with any degree of consistency. Alterations in the level of serum globulins have also been noted. In the majority of cases, gamma globulin is reduced and beta globulin elevated. Total protein values, on the other hand, are normal. It is of interest that the survival rate of radioactively labeled gamma globulin is shorter in patients with myotonic dystrophy than in normal persons[5].

Histopathologically, changes observed in this disease are similar to those seen in other types of muscular dystrophy—scattered enlargement of fibers, degeneration and centrally placed sarcolemmal nuclei. The two characteristic pathological features commonly seen in this disease are: (1) prominent, long chains of centrally placed nuclei in an apparently intact muscle fiber, and (2) striated annulets or "Ringbinden" in transverse sections. These pathological changes are probably the result of reorientation of peripherally placed myofibrils from a longitudinal direction to one in which the fibrils encircle the fiber shaft. Similar changes have been observed in the contraction band of aging normal muscle, but they appear to be much more pronounced and frequent in myotonic muscle fibers. Striated annulets are thought by some to be caused by excessive irritability of the muscle fibers. Another distinctive pathological change is the presence of sarcoplasmic masses or regions of sarcoplasm in the center of the fibers, which are devoid of myofibrils.

Myotonia acquisita. In addition to the above-described syndromes, myotonia has been noted as a minor manifestation in other muscle diseases. Thus, it has been described in cases of polymyositis,[6] where it is transitory in nature, disappearing as the disease progresses. It has also been recorded in cases of progressive muscular atrophy and also in rare instances of polyneuropathy. The delayed relaxation seen in myxoedema does not have either the clinical or the electromyographic characteristics of myotonia and is therefore referred to as "pseudomyotonia."

As was mentioned earlier, myotonia may be a feature of periodic paralysis. It has been consistently seen in association with the hyperkalemic form[7] of the disease. While myotonia is usually seen during episodes of weakness, sometimes it may be demonstrated only by electromyography. Myotonia has also been described in a case of hypokalemic periodic paralysis.[8]

Lastly, myotonia can be mistaken for a syndrome tentatively attributed to a reduction of muscle relaxing factor.[9] This entity is characterized by painless contraction and stiffness of muscles associated with electromyographic "silence" following exercise. Blood pyruvate and lactate levels before and after exercise performed under ischemic conditions are higher than in normal persons. Myophosphorylase activity is normal. Sarcoplasmic reticulum isolated from the muscles of such a patient reveals a decidedly reduced ability to take up calcium. This causes a delay

in relaxation and may be due to a deficiency of relaxing factor. In myotonia, slow relaxation is attended by visible and audible electromyographic activity.

Dr. Dreyfus: Thank you, Dr. Vijayan. I will now ask Dr. Bhatt to review for us the current pathophysiologic knowledge of myotonia.

Dr. Bhatt: It is perhaps best to begin by saying that pathophysiologically myotonia is as yet poorly understood. However, let us make an attempt to present a workable hypothesis based on available evidence.

To a considerable extent the experimental approaches to the understanding of myotonia have been helped by the availability of an animal model, a breed of goats native to certain parts of the southern United States that are subject to myotonia congenita.

As in all experimental neurology, some of the earliest methods of analysis were by the process of elimination. Procedures ranging from removal of the highest cortical centers to transsection of peripheral nerves were found to have no effect on myotonia. Therefore, it was surmised that the disease involved structures distal to the nerve. It remained for acquisition of the knowledge of the mode and site of action of curare to exonerate the end-plate from the list of potential culprits. The study of individual neuromuscular junctions in myotonia has added further evidence that presynaptic mechanisms, end-plate potentials, acetylcholine sensitivity, and acetylcholinesterase activity are normal.[10] These findings localize the search for the origin of myotonia to the muscle fiber.

Before proceeding further with our method of analysis, it may be useful to recapitulate briefly some of the biophysical processes involved in muscle contraction. First, the surface membrane of the muscle is depolarized. This depolarization then spreads into the interior of the fiber by means of a transverse tubular system, causing depolarization of the sarcoplasmic reticulum, another system of tubules which stores calcium. Release of calcium ions from the sarcoplasmic reticulum activates muscle contraction. Released calcium interacts with tropomyosin, one of the muscle proteins, with the subsequent formation of bridges between the contractile protein actin and another protein, myosin. This set of events leads to contraction of the muscle fiber. Relaxation, on the other hand, is probably the result of calcium being "soaked up" by the sarcoplasmic reticulum.

The basic defect in myotonia has not yet been clearly elucidated. The most probable cause of the phenomenon appears to be some physiologic alteration in the muscle membrane which renders it unduly sensitive to electrical, chemical and mechanical stimulation. More specifically, there may be defective depolarization. Other mechanisms which have been postulated are an inordinate propensity for actin and myosin to maintain bridges, resulting in prolonged contraction, or a failure in calcium uptake by the sarcoplasmic reticulum, resulting in delayed relaxation. However, biochemical and ultramicroscopic studies of myotonic muscle have revealed that the latter two mechanisms are entirely normal.

In lower animals, two types of muscle are found: white and red. The former are responsible for twitch contraction—that is, they respond to stimuli by a quick contraction. They have a well developed sarcoplasmic reticulum and abundant glycolytic enzymes for their anaerobic metabolism. The red fibers respond in a slower and more sustained manner. They have a poorly developed sarcoplasmic reticulum and depend on oxidative enzymes. All human muscles are mixed. Muscles which have a preponderance of white fibers have sarcoplasmic reticulum characterized by high levels of calcium and a rapid rate of uptake of this ion. In myotonic dystrophy, the initial rate of calcium uptake is higher than normal while the total uptake remains normal. This suggests that red fibers are involved predominantly.[11] This fact has been substantiated by histochemical studies.[12]

Another way to study a clinical condition is to produce the entity in normal experimental animals by means of exogenous factors. Myotonia develops both in humans and in experimental animals when they are treated with certain inhibitors of cholesterol biosynthesis[13,14].

The analogues of cholesterol which act by inhibiting the conversion of desmosterol (dehydrocholesterol) to cholesterol, tend to produce myotonia. These agents cause an increase in plasma desmosterol and a consequent fall in plasma cholesterol. On the other hand, agents which block the synthesis of mevalonic acid—a precursor of cholesterol—do not cause an increase in plasma

desmosterol; they reduce plasma cholesterol yet do not produce myotonia. Triparanol, a nonsteroid compound which increases plasma desmosterol and which reduces plasma cholesterol, does not produce myotonia. Therefore, in order to be a myotonogenic agent, the drug must be a steroid which causes an increase in desmosterol and a decrease in cholesterol levels. The structure activity relationship of these compounds seems to reside in their specific dialkylamino substituted steriod nucleus. Sophisticated studies have shown that at least some of these myotonia producing agents have been incorporated into the lipid portion of the red blood cell membrane. Granted that it is a far cry from the red blood cell wall to the membrane of an isolated muscle cell, a beginning appears to have been made.

From the physiological point of view, the upstroke of the action potential representing depolarization of a muscle fiber is due to a sudden increase in sodium permeability, while the downstroke is caused by a combination of decreased sodium and an increase in potassium permeability. During depolarization the sodium leaks into the cell and potassium leaks out; therefore, anything which prevents either the exclusion of sodium or the intrusion of potassium may lead to persistent depolarization. A malfunctioning sodium pump could prevent normal sodium potassium exchange and result in a high intracellular sodium concentration and an elevated extracellular potassium concentration.

Certain studies carried out in human myotonic dystrophic muscle have shown that there exists no difference between the sodium pump efficiency relative to that of normal muscle, while there is a difference between the steady or resting membrane potentials of normal and myotonic dystrophic muscle, the latter being somewhat less negative.[15] The alteration in the steady-state transmembrane potential has not been substantiated in myotonic goats.

Another cause of repetitive activity in skeletal muscle is an increase in the membrane resistance. Studies in myotonic goats have shown that while the fiber capacitance and myoplasmic resistance are normal, the membrane resistance is two and one half times that of normal goat muscle membrane.[16] The increased membrane resistance could conceivably be due to a decreased potassium permeability bringing about an ionic imbalance which could cause myotonia. This is known to occur in denervated muscle. Denervation, however, is rarely part of the disease in which myotonia is present. No definite decrease in potassium permeability has been demonstrated. Lipidy and Bryant[17] suspect that in goat myotonia the permeability to chloride may be decreased. No such dysfunction has as yet been conclusively demonstrated in human myotonic muscle.

TABLE 2.—*Effective Therapeutic Agents for Myotonia*

Diphenylhydantoin (Dilantin®)
Procainamide (Pronestyl®)
Quinine sulphate
Adrenocorticotropic hormone (ACTH)
Corticosteroids (cortisone)

From the above it may be inferred that the defect, whatever it is, probably resides in the membrane. In myotonic dystrophy and myotonia congenita there is no abnormality of the intracellular or extracellular ionic concentrations. In hyperkalemic periodic paralysis, while at certain times changes in potassium concentration are present, the myotonia often persists in the period between attacks, during which ionic concentrations are normal. Therefore, it is more likely that, rather than being causally related, hyperkalemia and myotonia are either independent phenomena or stem from a common defect. It is also likely that the precise muscle membrane defect or defects responsible for myotonia may be different in each clinical entity in which the symptom is encountered.

Dr. Dreyfus: Thank you, Dr. Bhatt. Now that we have considered the clinical and the pathophysiological aspects of myotonia, a few words should be said about its treatment. Since it is generally believed that myotonia is caused by a biophysical abnormality of the muscle membrane, therapeutic agents which stabilize or hyperpolarize the membrane or drugs which alter the ratio of extracellular to intracellular ions might be expected to bring about symptomatic relief. Drugs which have been used successfully for myotonia include diphenylhydantoin (Dilantin®), procainamide (Pronestyl®), quinine and adrenocorticotropic hormone (see Table 2). Of the various drugs used, Dilantin appears to be the most effective, the safest and the best tolerated. The mechanism of action of Dilantin in the treatment of myotonia remains essentially unknown. Experi-

mental evidence suggests, however, that the drug acts directly on the muscle fiber membrane by activating the sodium pump. The resultant extracellular sodium shift would tend to stabilize the membrane. Three hundred milligrams of Dilantin a day, given in divided doses, is effective, frequently without side effects of note. However, ataxia, bone marrow depression and proliferation of lymphoid tissue must be anticipated. Dilantin generally produces better results than does procainamide (Pronestyl®), which must be administered in large daily doses (3 to 4 grams) and which may produce unpleasant side effects such as insomnia, irritability, nausea and dyspepsia. In most patients, Pronestyl is more effective than is quinine. The latter, given orally, 500 to 1000 mg a day, frequently causes nausea, tinnitus, headaches and visual symptoms. Adrenocorticotropic hormone and cortisone are of doubtful value. However, they may reduce myotonia by altering the ratio of extracellular to intracellular potassium or sodium. In addition steroids may slow up the inexorable progress of the destructive process of myotonia dystrophy.

More specific treatment of myotonia awaits the elucidation of basic pathophysiology.

ACKNOWLEDGMENT: We wish to thank Dr. Ted N. Thompson for permitting us to examine and discuss his patient.

TRADE AND GENERIC NAMES OF DRUGS

Dilantin® ..... diphenylhydantoin
Pronestyl® ..... procainamide

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VASOCONSTRICTORS IN SHOCK?

In the surgical patients you see in shock, both from volume loss and from sepsis, do you use vasoconstrictors at any time?

"During the early stages of shock, the normal physiology is one of increasing activity of the sympathetic nervous system. That means, among other things, increased heart rate and increased vasoconstriction. It would seem very unreal to me to give a vasoconstrictor under those circumstances. The body is doing the best it possibly can; and it doesn't really benefit from any help.

"On the other end of the spectrum, when we're in the stage where shock has been going for a long time, and we're now getting into that loose unhinging of all mechanisms, it's conceivable that one should infuse a vasoconstrictor to help support the pressure."

—WILLIAM R. DRUCKER, M.D., Toronto

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